Feasibility of Partial Nephrectomy for Wilms' Tumor in Children With Beckwith-Wiedemann Syndrome Who Have Been Screened With Abdominal Ultrasonography

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Background: Children with Beckwith-Wiedemann syndrome (BWS), a congenital syndrome associated with Wilms' tumor commonly are screened with abdominal sonography resulting in detection of tumor at a lower stage. Wilms' tumors have been traditionally treated with complete nephrectomy; however, smaller tumors are amenable to nephron-sparing surgery. Because Wilms' tumors may be metachronous and nonmalignant disease may compromise renal function in BWS, nephron-sparing approaches may be desirable as the first option.

Methods: Seven patients with BWS and Wilms' tumor underwent nephrectomy. The preoperative computed tomography (CT) or ultrasound scan were evaluated by a pediatric surgeon to assess whether partial nephrectomy would have been feasible. The determining criteria included tumor involving one third or less of the kidney and no involvement of either hilar or vascular structures.

Results: Seven patients underwent complete nephrectomies. The remaining patient, who had undergone a left nephrectomy before the initiation of screening had salvage chemotherapy after biopsy results showed right kidney involvement with Wilms' tumor.

Conclusions: Nephron-sparing surgery is reasonable to consider in children with Beckwith-Wiedemann syndrome who are screened at intervals of 4 months or less. The relative benefits of partial nephrectomy for children with Wilms' tumor–predisposing conditions only can be assessed in the setting of a cooperative clinical trial.

INDEX WORDS: Beckwith-Wiedemann syndrome, Wilms' tumor, partial nephrectomy.

BECKWITH-WIEDMANN SYNDROME (BWS) is an inherited overgrowth condition associated with a predisposition to cancer, specifically embryonal tumors. Children with BWS present as neonates with macrosomia, macroglossia, and omphalocele. In addition, they may have one or more of the following features: neonatal hypoglycemia, organomegaly, hemihypertrophy, ear pits, or creases.[1] Wilms' tumor represents a common embryonal tumor of childhood with initial presentation at a median age of 3.5 years.[2] The approximate risk of developing Wilms' tumor or other malignancies in patients with BWS is 10% during the first decade of life.[3] Children with BWS are at increased risk of bilateral Wilms' tumor and metachronous Wilms' tumor when compared with the general population.[4,5] In addition, this population is at increased risk of nonmalignant renal disease. In the BWS registry, 38 (25%) of 152 patients with BWS had 45 nonmalignant abnormalities, including medullary renal cysts (n = 19, 13%), caliceal diverticula (n = 2, 1%), hydronephrosis (n = 18, 12%), and nephrolithiasis (n = 6, 4%). Thirty-three of the thirty-eight patients (87%) with nonmalignant renal disease were asymptomatic.[6] The 5 patients with symptomatic disease had renal calculi with subsequent progressive renal disease, frequent urinary tract infections, or infected renal cysts. The progressive nature of these lesions is yet to be determined, but progressive renal failure associated with medullary sponge kidneys has developed in several patients (DeBaun, unpublished data).

The critical question for patients with BWS, who are screened regularly for Wilms' tumor and who present with smaller Wilms' tumors than would be expected in a nonscreened population, is whether the benefits of nephron-sparing surgery outweigh any potential incremental decrease in survival. Before addressing this question, the feasibility of partial nephrectomy in this population must be addressed. We reviewed the renal imaging studies of children with Wilms' tumor and BWS who

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were screened systematically to determine whether they were candidates for a partial nephrectomy.

MATERIALS AND METHODS

The Beckwith Wiedemann Registry was established at the National Cancer Institute to estimate the age-specific incidence and relative risk of cancer in this population.[3] We used the following criteria to define registry eligibility: (1) physician's clinical diagnosis of BWS and (2) two of the following common features of BWS: macroglossia, large birth weight, neonatal hypoglycemia, ear creases or ear pits, and abdominal wall defect. Parents were contacted in writing to request access to the initial information gathered. The parents who consented to participate were mailed informed consent and medical information release documents. Any cancers reported were confirmed by medical record and pathology report review. Between April 1989 and January 1994, the registry accumulated 183 children who were evaluated over a total of 482 person-years. Nineteen patients with Wilms' tumor were found, 9 of whom had undergone screening at least every 4 months (Table 1). Two children had diagnosis shortly after birth and, therefore, were not screened. Eight children were either not screened at all or were screened at an interval greater than every 4 months. One child was screened and felt to be a partial nephrectomy candidate by the National Wilm's Tumor Study (NWTS) group. Because the films for the latter child were not available to us, we have limited the report to the 8 patients whose films we were able to review.

A uroradiologist reviewed all films for technical quality. A pediatric surgeon, who was unaware as to the actual surgery that the child had undergone, retrospectively reviewed the imaging studies. The surgeon was asked to categorize the patients as definitely, probably, or not a candidate for partial nephrectomy. Based on the available imaging studies, which included sonography of the kidney or computed tomography (CT) scan with contrast of the kidneys, the following criteria were used for preoperative selection of patients eligible for partial nephrectomy: confined tumor with at least two thirds of the kidney free of tumor and no involvement of hilar or vascular structures. Examples are shown in Figs 1-3.

RESULTS

The 8 patients screened with abdominal ultrasonography had an average tumor size of 3.3 cm compared with the average size of a Wilms' tumor, which is between 11 and 13 cm in patients who present with symptoms.[7] The surgeon believed that 5 children would have been definite candidates for partial nephrectomy, whereas 3 patients were probable candidates but would require intraoperative assessment to be certain of whether there was involvement of hilar or vascular structures. Seven patients had complete nephrectomies. The remaining patient, who had undergone a left nephrectomy before the initiation of screening, had salvage chemotherapy only, after biopsy results showed right kidney involvement with Wilms' tumor.

Table 1. Clinical Features of Screened (With Sonography) Patients With BWS and Wilms' Tumor

Patient No.	Age at Diagnosis	Kidney	Location	Size (cm)	Screened	PN Candidate
1	7 mo	Right	Mid	2.5	Yes	Yes
2	8 mo	Right	Lower	1.9	Yes	Yes
3	25 mo	Right	Upper	3.0	Yes	Possible
4	24 mo	Left	Mid	2.0	Yes	Yes
5	10 mo	Right	Lower	2.5	Yes	Yes
6	17 mo	Left	Upper	3.5	Yes	Possible
7	15 mo	Left	Mid	5.4	Yes	Yes
		Right	Lower	2.8	Yes	Yes
8	71 mo	Right	Lower	3.0	Yes	Possible*

*This patient had Wilms' tumor that was detected in the left kidney before the initiation of screening. The right sided lesions were detected in the left kidney before the initiation of screening. The right sided lesions were detected on screening sonography at 4-month intervals initiated after the left nephrectomy.

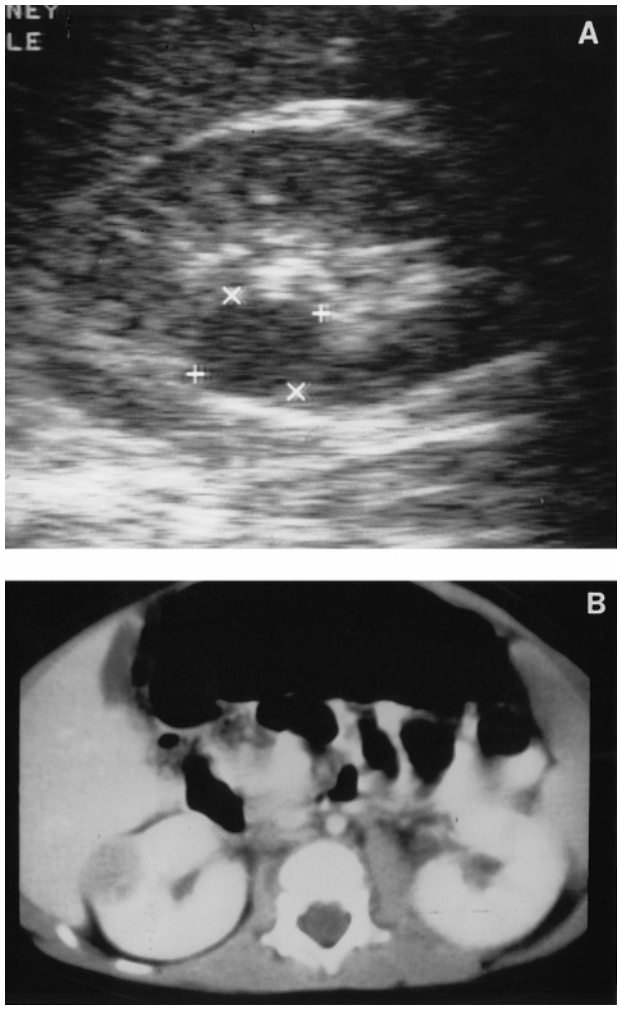

Fig 1. Eighteen-month-old boy with BWS. Screening ultrasonography (A) shows small Wilms' tumor in right kidney that is confirmed on the CT (B). This tumor is amenable to partial nephrectomy.

DISCUSSION

Children with BWS are at risk for cancers, especially Wilms' tumor. The risk of metachronous tumor development appears higher in this population when compared with the general population.[5] In children with BWS

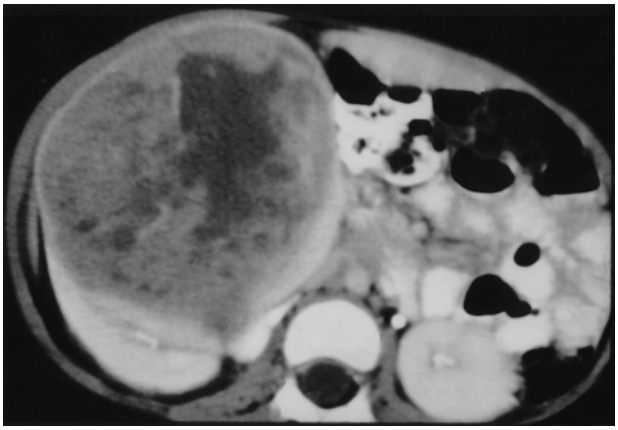

Fig 2. Four-year-old boy with BWS who, although not one of the patients described in this study, has an 11-cm Wilms' tumor in the right kidney with areas of necrosis. A partial nephrectomy would be considered impossible in this patient.

screened on a regular basis, we found that partial nephrectomy is reasonable in select patients. The benefit of routine screening for early detection of Wilms' tumor in the BWS patient population has been reported previously.[8]

Given the high success rate of complete nephrectomy coupled with chemotherapy and radiation therapy if needed, why should we consider nephron-sparing approaches in children with BWS? There are 3 major reasons for addressing the issue of whether a partial nephrectomy should be considered in a trial setting for children with Wilms' tumor cancer predisposition syndromes.

A primary reason for consideration of partial nephrectomy in this population is that most children in the United States with BWS are screened with sonography of the kidneys, at least every quarter, resulting in a considerably smaller tumor size at the time of diagnosis than children with sporadic Wilms' tumor.[8] Smaller tumors are amenable to partial nephrectomy assuming that they do not involve hilar or vascular structures.

A second reason for raising the possibility of a partial nephrectomy is the increased risk of metachronous Wilms' tumor in children with BWS. Children with perilobar rests, the most common type of nephrogenic rests occurring in children with BWS, have approximately a 6-fold risk of metachronous Wilms' tumor when compared with the reference group, children with sporadic Wilms' tumor without nephrogenic rests.[5] Persons with both perilobar and intralobar rests have approximately an 18-fold risk using the same reference group.[5] Additionally, children with nephrogenic rests who are less than 12 months of age have the highest risk of metachronous Wilms' tumor.[5] One of the patients in this series had metachronous Wilms' tumor after a complete resection was performed on the initial Wilms' tumor, and 3 patients were less than 12 months, raising the possibility of an increased risk for metachronous Wilms' tumor in the future.

A third reason for considering partial nephrectomy is that increasing evidence shows that some patients with BWS may have progressive renal disease. Approximately 25% of BWS patients have nonmalignant renal abnormalities categorized as medullary cysts, caliceal diverticula, hydronephrosis, and nephrolithiasis.[6] These anatomic anomalies may lead to later renal complications owing to repeated infection, nephropathy related to persistent reflux, or medullary sponge kidney. The presence of nonmalignant renal abnormalities does not preclude the possibility of renal malignancy in the ipsilateral or contralateral kidney. However, the presence of these types of abnormalities in this patient population underscores the need to preserve renal function as much as possible.[6]

Partial nephrectomy is performed commonly in patients who present with bilateral Wilms' tumor in the United States or in selective series in Europe where chemotherapy is administered before surgery. The Fourth National Wilms' Tumor study evaluated patients who underwent partial nephrectomies. The follow-up period for this series was 3.6 years with an overall survival rate of approximately 80% at 4 years. Less than 10% of the kidneys that had undergone renal salvage had evidence of local recurrence. The rate of local tumor recurrence after renal salvage was comparable with that of patients that had gross tumor remaining after the operation (8.5% *v* 9%). Only 3 of the 19 kidneys with positive tumor margins showed local recurrence. The investigators suggest that the presence of positive or negative margins may not influence local recurrence or

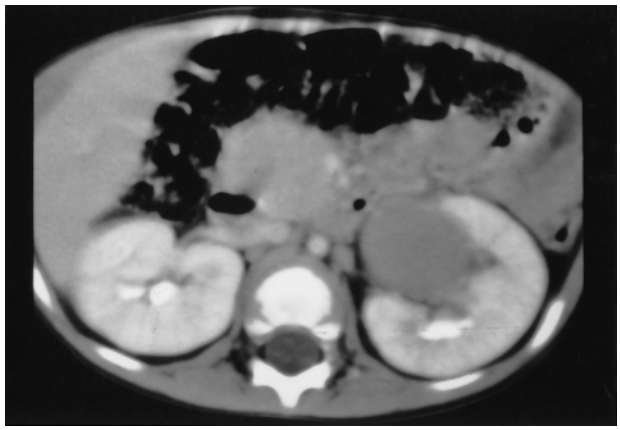

Fig 3. Twenty-three–month-old boy with BWS who has a 3-cm left hilar Wilms' tumor. This is an example of a mass that potentially could be amenable to partial nephrectomy, but the decision would have to be made intraoperatively.

survival as much as has been though.[9] A retrospective analysis designed to evaluate partial nephrectomy in sporadic Wilms' tumor patients used the following criteria for preoperative selection: functioning kidney, tumor confined to upper or lower pole with at least two thirds of the kidney being without evidence of tumor, no involvement of hilar or vascular structures. Statistical analysis comparing surgical and pathologic findings related to the feasibility of partial nephrectomy compared with preoperative radiologic prediction showed a sensitivity of 80% with a specificity of 97%.[10]

Children with BWS represent a unique group at increased risk of metachronous tumor or other nonmalignant renal complications. Our results provide a reasonable starting point to consider partial nephrectomy in a screened population of at risk children. Partial nephrectomy is only justified if the disease-free survival rate does not decrease, and the quality of life is prolonged because of more functional renal parenchyma. Only in a prospective clinical trial setting supported by the NWTS of North America and other collaborative Wilms' tumor study groups would there be sufficient number of patients to assess the utility of partial nephrectomy with Wilms' predisposition syndromes.

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